

CRT Licensing Opportunity



Therapeutic HPV Vaccine

- Strong patent portfolio protects the HPV subunit vaccine comprising of HPV16 L2/E6/E7 proteins
- Phase I safety and immunogenicity studies show L2/E6/E7 to be well tolerated and immunogenic
- Phase II prime-boost studies demonstrated clear clinical responses in patients with AGIN
- Potential utility as therapeutic/prophylactic combination vaccine

BIOLOGICAL THERAPEUTICS | Clinical Phase II

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Summary

A human papillomavirus (HPV) vaccine has been designed (in collaboration with Xenova) for the treatment and/or prevention of HPV-related diseases including vulval, anal and cervical intraepithelial neoplasias and cervical cancer. The vaccine comprising L2/E6/E7 proteins from HPV16 was designed to generate a strong cellular immune response against HPV-infected cells. Clinical trials have shown L2/E6/E7 to be immunogenic with some clinical responses. More recently HPV16 L2/E6/E7 has been shown to induce L2-specific serum antibodies that neutralised across papillomavirus species (1). A further Phase II trial of the vaccine in combination with a topical adjuvant began Spring 2006 and is now being completed.

Cancer Research Technology (CRT) is currently seeking a commercial partner to further develop this promising therapeutic vaccine. A strong patent portfolio, materials (e.g. cell banks) and know-how (e.g. process, regulatory) are available for licensing from CRT.

Background

Cervical dysplasia (also known as cervical intraepithelial neoplasia, CIN) is one of a group of conditions, including VIN (vulval intraepithelial neoplasia), known collectively as anogenital intraepithelial neoplasia (AGIN). These conditions are precursors to invasive cancers. In a significant proportion of patients CIN progresses to cervical cancer, which is one of the main causes of cancer-related death for women under the age

of 40 worldwide. The WHO reported that cervical cancer has an incidence of 500 000 new cases in the world each year, of which 45% result in death. It is estimated that approximately 1-2% of women worldwide suffer from CIN. VIN is a chronic, relapsing condition in which conventional surgical treatment is disfiguring and often of limited therapeutic benefit. The incidence of VIN has increased over the last 20 years, particularly in younger women. There is clearly a medical requirement for novel treatments of AGIN disease.

The cost burden of both treatment and monitoring of women with CIN is substantial. The direct cost of CIN in the US is \$1.6 billion. Large potential markets also exist in India, SE Asia, Central and South America.

The causal link between oncogenic HPV and the development of AGIN conditions is well established (2) and there is strong evidence that the induction of a cell-mediated immune response against HPV antigens would lead to the elimination of infected cells. Published data have reported that tumour cells in more than 90% of patients with cervical cancer contain DNA from the HPV virus, specifically types 16 and 18.

Development of L2/E6/E7 Vaccine

The L2/E6/E7 subunit vaccine comprising proteins from HPV16 was designed to generate a strong cellular immune response against HPV-infected cells. The choice of antigens has been based on therapeutic vaccination studies in animal models.

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HPV oncogenes E6 and E7 are expressed throughout HPV-associated AGIN and offer attractive targets for immunotherapy as they are exclusively expressed in virally-infected neoplastic cells. A number of animal models have shown that the induction of E6- and/or E7-specific T-cells by vaccination can effectively control established tumours (3). The L2 capsid protein is critical for papillomavirus infection: an L2 fusion protein of therapeutic interest was found to be highly effective in promoting tumour rejection in animals with massive infiltration of lymphocytes in the tumours (4).

Pre-Clinical Data

L2/E6/E7 was shown to elicit HPV 16-specific cytotoxic T-cells, T-helper cells and antibodies in a mouse HPV16 TC-1 tumour xenograft model (5). Proof-of-principle experiments demonstrated that treatment with L2/E6/E7 prevented tumour outgrowth and extended symptom-free survival in mice.

Treatment with L2/E6/E7 vaccine prevents tumour outgrowth and prolongs symptom-free survival in a murine model of HPV disease.

Recent primate in vivo data have shown that administration of L2/E6/E7 can effectively neutralise not only HPV16 but also other high risk HPV genotypes including HPV18, HOV31, HPV45, HPV58, as well as HPV6 and HPV11. Vaccination with L2/E6/E7 completely prevented tumour growth after challenge with HPV16 - transformed TC-1 tumour cells (8).

Clinical Data

In a Phase I double-blind, placebo-controlled, randomised dose escalating trial, L2/E6/E7 was found to be safe and immunogenic in a dose dependent manner. The vaccine was administered by intramuscular injection to 40 healthy volunteers. L2/E6/E7 vaccine was well tolerated and no serious adverse events were reported during the study. L2/E6/E7-specific antibody responses and positive T-cell responses were seen in all of the cohorts receiving active vaccine.

In addition, L2/E6/E7 has been evaluated in AGIN patient populations in prime boost strategies, in combination with TA-HPV (a live recombinant vaccinia expressing E6 and E7 from HPV 16 and HPV 18). L2/E6/E7 has been tested as either the prime or boost vaccine (6, 7). Both regimes demonstrated L2/E6/E7 to be immunogenic and showed some clear clinical responses even in women with long-standing disease. A further Phase II trial of L2/E6/E7 in combination with a topical adjuvant began Spring 2006.

Manufacturing Process

The L2/E6/E7 vaccine is produced in *E. coli* and purified using a proprietary downstream GMP-compatible process. Well validated analytical assays are also in place.

Patent Portfolio

- HPV fusion polypeptides & compositions
WO 96/26277
Granted US; Europe/Japan pending
- Papillomavirus L2 Protein in therapeutic vaccines
WO 93/00436
Granted US, Europe, Australia, Hong Kong, Japan
- Purification of biological preparations (endotoxin removal)
WO 00/59927
Granted US; Europe/Japan/Canada pending

Publications

1. Gambhira *et al.* 2006 *Cancer Res.* **66**:11120-11124
2. zur Hausen 1991 *Science* **254**: 1167-1173
3. McNally *et al.* 2002 *Int. J. Gynecol. Cancer* **12**: 490-495
4. Jarrett *et al.* 1991 *Virology* **184**: 33-42
5. van der Burg *et al.* 2001 *Vaccine* **19**: 3652-3660
6. Smyth *et al.* 2004 *Clin. Cancer Res.* **10**: 2954-2961
7. Davidson *et al.* 2004 *Vaccine* **22**: 2722-2729
8. Karanam *et al.* Unpublished Data

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